IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Boussiotis et al.

Serial No.: 08/270,152

Filed: July 1, 1994

For: METHODS FOR MODULATING T CELL RESPONSES BY MANIPULATING A COMMON CYTOKINE RECEPTOR GAMMA CHAIN

Attorney Docket No.: RPI-022

Group Art Unit: 1642

Examiner: Gambel, P.

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REPLY BRIEF PURSUANT TO 37 C.F.R. 1.193(b)(1)

In response to the Examiner's Answer dated March 17, 1998 Appellants submit a revised "Statement of Issue Presented for Review" (subsection VI) to be substituted for subsection VI of the Appeal Brief filed December 16, 1997. In addition, Appellants submit further remarks with respect to "Arguments" (subsection VIII) which are responsive to the Examiner's Answer and are supplemental to the remarks already made of record in subsection VIII of the Appeal Brief filed on December 16, 1997.

VI. STATEMENT OF ISSUE PRESENTED FOR REVIEW

Appellants present the following issue for review:

I. Whether claims 48, 50, 55-61, and 98 are unpatentable under 35 U.S.C. § 112, first paragraph, as failing to be adequately described or enabled by the disclosure.

VIII. ARGUMENTS

Rejection of Claims 48, 50, 55-61, and 98 Under 35 U.S.C. § 112, First Paragraph

The Examiner maintains his rejection of claims 48, 50, 55-61, and 98 under 35 U.S.C. §112, first paragraph. In support of his position that claims 48, 50, 55-61 and 98 are not enabled by the disclosure, the Examiner relies on (A) Baskar et al. *PNAS* 90:5687-5690 (1993); (B) Boussiotis et al. *Science*, 266:1039-1042 (1994); (C) Boussiotis et al. *Research in Immunology* 146:140-149 (1995); (D) Bluestone *Immunity* 2:555-559 (1995); and (E) Russell et al. *Science* 262:1880-1883 (1993).

However, Appellants respectfully submit that the Examiner has improperly relied on evidence ***after*** Appellants filing date to establish that the claims on appeal are not enabled by the disclosure. See e.g., *In re Hogan* 559 F.2d 595, 194 USPQ 527 (C.C.P.A. 1977) in which the court held that "it is improper to consider developments in the art ***after the applicant's effective filing date*** as evidence to prove that the original application disclosure was non-enabling". Accordingly, the Examiner has improperly relied on the teachings of Boussiotis et al. (*Science*, 266:1039-1042 (1994)), Boussiotis et al. (*Research in Immunology* 146:140-149 (1995)) and Bluestone (*Immunity* 2:555-559 (1995)).

In view of this, the Examiner may only rely on Baskar et al. (*PNAS* 90:5687-5690 (1993)) and Russell et al. (*Science* 262:1880-1883 (1993)), which Appellants submit fail to support the Examiner's position that the claimed methods, which target the γ chain with

anti-γ chain antibodies to thereby stimulate T cells, including anergic T cells via costimulatory molecules, are unpredictable. In fact, Baskar et al., was cited by Appellants in support of the therapeutic utility of the claimed methods. Moreover, Russell et al., the only evidence relied on by the Examiner which was available at the time of Appellants' filing date, teaches that the IL-2R gamma chain is a functional component of the IL-4 receptor and is associated with the IL-7 receptor. Based on this observation, Russell et al. conclude that this finding "begins to elucidate why deficiency of the common gamma chain (gamma c) has a profound defect on lymphoid function and development, as seen in x-linked severe combined immunodeficiency." As such, Russell et al. is not relevant to the issue of enablement of the presently pending claims on appeal, which are directed to methods for stimulating T cell responsiveness by the use of anti-γ chain antibodies which bind to and transduce a signal via the γ chain such that T cell responsiveness is stimulated.

With regard to the issue of enablement of the claims on appeal, the Examiner is of the opinion that stimulating T cells and anergic T cells via costimulatory molecules, including targeting the γ chain with anti-γ chain antibodies, is unpredictable. In particular, the Examiner asserts that "Appellant's stimulation of T cells with anti-γ chain antibodies requires cross-linking (e.g. via rabbit anti-mouse Ig) in the presence of T cell receptor signaling (see Example 2 on page 23 of the specification)" and that "[t]he specification does not provide sufficient information how to achieve such cross-linking in vivo."

Thus, the Examiner recites the sole issue for appeal as follows:

> ***"[t]he issue involved is whether or not the evidence of record [sic] based on in vitro studies is generally recognized by those of ordinary skill in the art as being reasonably predictive of success in the practical in vitro and in vivo therapeutic methods encompassed by the instant claimed methods."***

As stated by the court in *In re Wands*, a conclusion of lack of enablement requires that evidence regarding each of the following factors be considered: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404. It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The Examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id.* at 737 and 740, 8 USPQ2d at 1404 and 1407.

Appellants respectfully submit that the Examiner has improperly relied on the "unpredictability" in the art and has failed to adequately consider the evidence with respect to the remaining factors, specifically, (1) the breadth of the claims as amended and presently on appeal, (2) the amount of direction provided by the inventor, (3) the existence of working examples, and (4) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Each of these factors, as well as the level of predictability in the art, is addressed below.

First, the claims on appeal are not unduly broad and are directed to the use of an agent, an anti-γ chain antibody, to stimulate T cell responsiveness by binding to and transducing a signal via the γ chain such that T cell responsiveness is stimulated.

With regards to the amount of direction provided by the inventor, Appellants respectfully submit that the specification contains sufficient teachings as to the nature of the anti-γ_c antibody, methods for preparing the antibody, and suitable formulations for administering the antibody to a subject. For example, on page 6, lines 15-21 a "stimulatory form" of an anti-γ_c antibody is described. The specification teaches that the

anti-γ_c antibody can be a soluble antibody that is cross linked, e.g., by a secondary antibody, or it can be an immobilized form of an antibody, e.g., an antibody bound to a solid support, such as a culture plate or bead. Moreover on page 6, line 22 through page 12, line 15, methods for preparing the anti-γ_c antibodies, e.g., humanized antibodies, are described. Finally, on page 18, line 16 through page 20, line 20, appropriate formulations for the delivery of the antibody into a subject, as well as doses, and duration of administration, are described.

Third, Appellants' disclosure provides specific, working examples demonstrating that agents within the scope of Applicants claim prevented the induction of T cell anergy in a human alloantigen specific T cell clonal model system. Specifically, Appellants demonstrated that antibodies directed against the common γ chain shared by IL-2, IL-4, and IL-7 receptors ($\alpha\gamma_c$) cross linked with rabbit anti-mouse Ig (RaM) or biotinylated, prevented the induction of anergy in human T cells and resulted in both proliferation and IL-2 secretion in the T cells upon re challenge, comparable to that observed with non-anergized control cells (see Example 2 on page 23). This data, in addition to the teaching provided in Appellants' disclosure, is more than reasonably indicative of *in vivo* efficacy as asserted and claimed by Appellants. Human T cells and the cell lines described in the disclosure are routinely used to mimic the immune system *in vitro* and are art-accepted models of *in vivo* therapeutic efficacy.

In addition, although the Examiner agrees that "the instant specification discloses that anti-γ chain antibodies can serve to stimulate signaling via the cytokine receptor gamma chain", he improperly concludes that "***provided that*** the antibody is cross linked either by secondary antibodies or bound to a solid support." In fact, Appellants' disclosure teaches that "[i]n one embodiment, the stimulatory form of anti-γ_c antibody is a soluble antibody that is cross linked, e.g., by a secondary antibody" and that "[i]n another embodiment, the stimulatory form of anti-γ_c is an immobilized form of an antibody, e.g., an antibody bound to a solid support, such as a culture plate or bead."

Thus, the specification teaches various forms of anti-γ chain antibodies which can be used in the claimed methods.

In fact, it was well known in the art at the time of Appellants invention that antibodies do cross link their "immunogens" *in vivo* without the need for an exogenous agent. For example, Goroff D.K. et al. (1991) *J. Immunol.* 146 (1):18-25 (submitted herewith as Appendix A, A1-A8) demonstrate that injection of mice with a foreign, polyclonal antibody to IgD sequentially induces: 1) activation of B cells by cross-linking of their cell membrane (m) IgD; 2) B cell processing and presentation of the bound anti-IgD antibody to T cells; 3) activation of these T cells; and 4) T-dependent stimulation of B cell differentiation into IgG1 secreting cells. In addition, a review article (Yashwant M.D. et al. (1997) *Immunol. Today* 18:127-1135, a copy of which is enclosed herewith as Appendix A, A9-A18) describes *in vivo* studies with monoclonal antibodies, indicating that these monoclonal antibodies (i.e., anti-Fcγ receptor antibodies) cross link with receptors (i.e., Fcγ receptors) *in vivo* (see in particular page 129 and references 19, 21, 22, and 25). Appellants further submit herewith (as Appendix B) a copy of press releases for IDEC Pharmaceuticals Corporation, a company in the business of producing antibodies for the treatment of a variety of human diseases, describing the successful use of antibodies in human clinical trials as at the time of Appellants' invention.

With respect to the methods for stimulating responsiveness in an anergic T cell (claim 98), the Examiner asserts that

> such anergic cells are refractory to stimulation via costimulation (see Boussiotis et al., Research in Immunology, 1995; particularly pages 144-146). Appellant's disclosed Examples rely upon T cells and not anergic T cells. Further appellant has not provided objective evidence to support the ability of stimulating anergic T cell responsiveness either in vitro or in vivo.

Appellants respectfully submit that in contrast to the Examiner's assertion, anergic cells are <u>not</u> refractory to stimulation via costimulation. In particular, Boussiotis et al.

teach that anergized T cells respond to co-stimulation following culture with a cytokine, e.g., IL-2 (see page 144, second column, second full paragraph). Thus, using appropriate conditions, anergic T cells can be stimulated to respond.

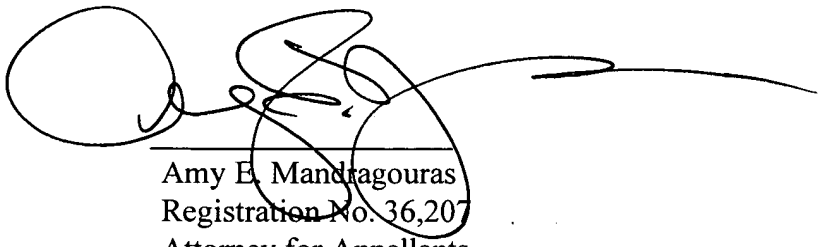
Finally, Appellants respectfully submit that enablement is not precluded even if some experimentation is required, provided that the amount of experimentation needed is not unduly extensive. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1567, 224 USPQ 409, 413 (Fed. Cir. 1986). Appellants have provided specific, working examples demonstrating that agents within the scope of Appellants claims prevented the induction of T cell anergy in a human alloantigen specific T cell clonal model system (see Examples 1 and 2 on pages 21 and 23, respectively). The data presented in the specification, in light of the teachings of the art at the time of Appellants invention, is more than reasonably indicative of *in vivo* efficacy as asserted and claimed by Appellants.

In view of the considerable direction provided by Appellants described above, as well as the working examples and state of the art with respect to antibody therapy in humans as illustrated in the evidence provided by Appellants (Appendices A and B), the ordinarily skilled artisan would not have been required to use "undue experimentation" to practice the claimed invention. Thus, the ordinarily skilled artisan, following a careful reading of the above-described teachings from Appellants' specification can make and use the claimed invention. Accordingly, it is respectfully submitted that claims 48, 50, 55-61 and 98 are fully enabled by the disclosure.

CONCLUSION

Appellants submit that claims 48, 50, 55, 56-61, and 98 meet the requirements of 35 U.S.C. §112, first paragraph and the Board is respectfully requested to reverse the final rejection of the claims for the reasons set forth above.

Respectfully submitted,



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